When “Good” Drugs go Bad

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November 2007

Declaration

- I have no conflicts of interest to declare.

Learning Objectives

- To provide an overview and summary of the current state of post-marketing surveillance in Canada.
- To review recent cases of adverse reactions occurring in different drug classes after the drugs have been marketed.
- To highlight the importance of adverse drug reaction surveillance programs.

Outline

- Health Canada Notifications 2007
  - Telithromycin
  - Pergolide
  - Glitazones
- Adverse Drug Reaction Reporting
- Questions

Telithromycin

Telithromycin

- Class
  - Ketolide
- Approved Indications
  - Community-acquired pneumonia (mild-moderate)
  - Acute bacterial exacerbation of chronic bronchitis
  - Tonsillitis/pharyngitis
- Dosing
  - 800mg po once daily x 5-10 days
- NOC: May 28, 2003

The Ketolides Drugs 2002; 62(12): 1771-1804
www.pmprb-cepmb.gc.ca

Adverse Effects

- Most common occurring in 8-10% of patients:
  - Diarrhea
  - Nausea
- Safety study of 12 000 patients:
  - Adverse events similar to comparator
  - Visual disturbances occurred in 0.6% of exposed pts
    - Blurred vision, diplopia, and accommodation difficulties

Ann of Intern Med 2006; 144(6) 447-448.

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Adverse Effects

"In clinical trials, increases in liver enzymes (AST, ALT, ALP) have been reported. The overall frequency of transaminase increases was similar to that seen in comparators. Elevations above 3x ULN were uncommon. The significance of these findings is unknown. Liver enzyme increases were usually asymptomatic and reversible."

www.sanofi-aventis.ca

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Health Canada Endorsed Important Safety Information on KETEK (telithromycin)

sanofi aventis

2006/09/29

Dear Health Care Professional:

Subject: **Updated safety information on KETEK (telithromycin) and hepatic events, aggravation of myasthenia gravis and syncope**

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/ketek_hpc-cps_e.html

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Brief Communication: Severe Hepatotoxicity of Telithromycin: Three Case Reports and Literature Review.

- Description of 3 cases of hepatotoxicity secondary to telithromycin
  - 1 pt spontaneously recovered
  - 1 pt required a liver transplantation
  - 1 pt died

Ann Intern Med 2006; 144: 415-420.

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Table. **Reported Hepatotoxicity in Head-to-Head Trials Involving Telithromycin***

Study, Year (Reference)	Comparator	Indication	Patients, *n*	Total Rate of Adverse Events in the Telithromycin Group versus the Comparator Group, %/%	Hepatic Adverse Events with Telithromycin versus the Comparator	
					Events, *n*/*n*	Description
Hagberg et al., 2002 (2)	High-dose amoxicillin	CAP	404	55.3/45.9	17/14	Abnormal results on liver function tests; ALT level increased to 3 × ULN
Norrby et al., 2001 (12)	Penicillin V	Tonsillitis or pharyngitis	395	35.4/35.2	0/1	ALT level increased to 3 × ULN
Luterman et al., 2003 (10)	Amoxicillin–clavulanate	Sinusitis	754	42.2/46.9/42.9†	NA	No hepatic differences between groups
Quinn et al., 2003 (14)	Clarithromycin	Tonsillitis or pharyngitis	463	67.2/57.5 ($P < 0.05$)	1/0	ALT, AST, and LDH levels increased 2.9, 7.6, and 2.5 × ULN, respectively
Buchanan et al., 2003 (9)	Cefuroxime	Sinusitis	593	36.1/31.4	NA	No hepatic differences between groups
Pullman et al., 2003 (13)	Trovafloxacin	CAP	223	47.2/33.0 ($P = 0.038$)	5/0	Abnormal results on liver function tests; AST level increased to 3 × ULN
Zervos et al., 2003 (15)	Cefuroxime	Acute exacerbation of chronic bronchitis	373	30/32.3	1/0	ALT level increased to 3 × ULN
Mathers Dunbar et al., 2004 (11)	Clarithromycin	CAP	416	57/49	1/0	ALT level, 418 U/L; AST level, 295 U/L
Aubier et al., 2002 (16)	Amoxicillin–clavulanate	Acute exacerbation of chronic bronchitis	325	23.8/36.9 ($P = 0.015$)	NA	No laboratory safety differences between groups
Ferguson et al., 2004 (17)	Moxifloxacin	Sinusitis	349	34.7/27.8	NA	No hepatic differences between groups
Tellier et al., 2004 (18)	Clarithromycin	CAP	575	44.6/44.9	10/7	Elevated levels of ALT and AST

Ann Intern Med 2006; 144: 415-420.

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Health Canada Endorsed Important Safety Information on KETEK® (telithromycin)

sanofi aventis

August 30, 2007

Dear Health Care Professional:

Subject: **REMOVAL OF SINUSITIS, BRONCHITIS AND TONSILLITIS/PHARYNGITIS INDICATIONS FOR KETEK® (telithromycin)**

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/ketek_2_hpc-cps_e.html

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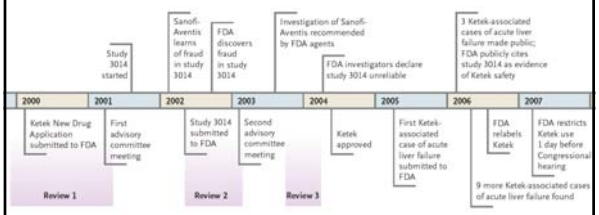
Telithromycin Timeline



NEJM 2007; 356(16): 1601-1604.

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Telithromycin Conclusion

- Contraindicated
  - Previous history of hepatitis and/or jaundice on a macrolide
  - Monitor pts for symptoms of hepatitis
- Removal of indications for:
  - Sinusitis, bronchitis, and tonsillitis/pharyngitis

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Pergolide

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Pergolide

- Class
  - Dopamine Agonist (Ergot)
- Approved Indications
  - Treatment of Parkinsons Disease
- Dosing
  - 0.05mg/day up to 5mg/day in 3 divided doses
- NOC:
  - 1991

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Health Canada Santé Canada

Health Products and Food Branch
Direction générale des produits de santé et des aliments

The Marketed Health Products Directorate (MHPD), Therapeutic Products Directorate (TPD) and Biologics and Genetic Therapies Directorate (BGTD) post safety alerts, public health advisories, press releases and other notices from industry as a service to health professionals, consumers, and other interested parties. Although MHPD, TPD and BGTD approve therapeutic products, MHPD, TPD and BGTD do not endorse either the product or the company. Any questions regarding product information should be discussed with your health professional.

This is duplicated text of a letter from Eli Lilly Canada Inc. and Draxis Health Inc.
Contact the company for a copy of any references, attachments or enclosures.

DRAXIS

Lilly

April 14, 2003

IMPORTANT SAFETY INFORMATION REGARDING PERMAX® (pergolide mesylate) and CARDIAC VALVULOPATHY

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Health Canada-Mandated Important Safety Information on PERMAX® (pergolide mesylate)

Lilly

August 10, 2007

Dear Health Care Professional:

Subject: Cease Sale of Permax® (pergolide mesylate) in Canada as of August 30, 2007

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/permax_3_hpc-cps_e.html

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Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation.

- Objective
  - To investigate the risk of newly diagnosed cardiac-valve regurgitation associated with the use of different dopamine agonists.
- Design
  - Cohort study with nested case-control analysis
- Population
  - United Kingdom General Practice Research Database
- Funding
  - Canadian Foundation for Innovation; Canadian Institutes of Health Research; unrestricted grant from Schering

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N Engl J Med 2007; 356: 29-38.

Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation.

- Inclusion
  - 40-80 years of age
  - 2 prescriptions for antiparkinsonian medications between Jan 1/98 – Aug 31/2005
- Exclusion
  - History of rheumatic heart disease, congenital heart disease, CHF, dilated cardiomyopathy, endocarditis or myocarditis, the carcinoid syndrome, IV drug use, heart-valve abnormalities
  - Use of the following medications: fenfluramine, dexfenfluramine, phentermine, ergotamine, dihydroergotamine, methysergide

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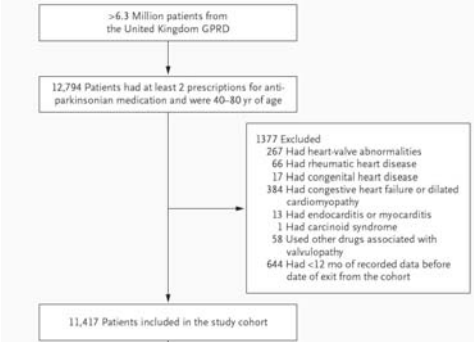
N Engl J Med 2007; 356: 29-38.

Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation.



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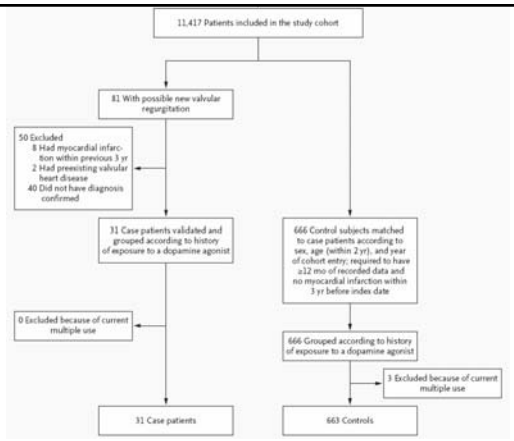
N Engl J Med 2007; 356: 29-38.



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Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation.

Table 3. Current Use of Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation.

Exposure	Case Patients (N=31)	Controls (N=663)	Adjusted Incidence-Rate Ratio (95% CI)*
	no. (%)		
No current or recent use of a dopamine agonist†	19 (61)	530 (80)	1.0
Bromocriptine	0	19 (3)	
Cabergoline	6 (19)	34 (5)	4.9 (1.5–15.6)
Pergolide	6 (19)	26 (4)	7.1 (2.3–22.3)
Lisuride	0	1 (0)	
Pramipexole	0	23 (3)	
Ropinirole	0	23 (3)	

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N Engl J Med 2007; 356: 29-38.

Table 4. Influence of the Daily Dose of Pergolide or Cabergoline and the Cumulative Duration of Use on the Risk of Cardiac-Valve Regurgitation.

Exposure	Case Patients (N=31)	Controls (N=663)	Adjusted Incidence-Rate Ratio (95% CI)*	P Value†
	no. (%)			
No current or recent use of a dopamine agonist‡	19 (61)	530 (80)	1	
Last daily dose				
Pergolide				0.07
≤3 mg	3 (10)	21 (3)	5.1 (1.3–20.4)	
>3 mg	3 (10)	5 (1)	37.1 (5.1–270.6)	
Cabergoline				0.01
≤3 mg	2 (7)	31 (5)	2.6 (0.5–12.8)	
>3 mg	4 (13)	3 (0)	50.3 (6.6–381.4)	
Cumulative duration of use				
Pergolide				
<6 mo	0	4 (1)		
≥6 mo	6 (19)	22 (3)	9.8 (2.9–33.1)	
Cabergoline				
<6 mo	0	11 (2)		
≥6 mo	6 (19)	23 (4)	7.8 (2.2–27.4)	

Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation.

Author's Conclusions:

"use of the dopamine agonists pergolide and cabergoline was associated with an increased risk of newly diagnosed cardiac-valve regurgitation"

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N Engl J Med 2007; 356: 29-38.

Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease.

- Objective
  - To assess the prevalence of valvular disease in pts treated w/ ergot-derived dopamine agonists through echocardiography.
- Design
  - Convenience sample
- Population
  - Outpatients of the Parkinson Institute (single hospital) in Milan
- Funding
  - Italian Parkinson Association, the Grigioni Foundation for Parkinson's Disease, and Isituti Clinici di Perfezionamento, Milan.

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N Engl J Med 2007; 356: 39-46.

Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease.

- N=255
  - 90 control subjects
  - 155 comparator subjects
    - 64 pergolide pts
    - 49 cabergoline pts
    - 42 non-ergot-derived dopamine agonists
- Results
  - Clinically important regurgitation
    - 23% pergolide (p=0.001)
    - 29% cabergoline (p<0.001)

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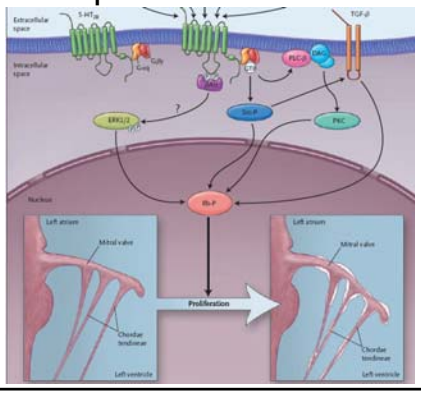
N Engl J Med 2007; 356: 39-46.

Proposed Mechanism



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NEJM 2007; 356(1): 6-9.

Pergolide Conclusion

- Sales ceased Aug 30, 2007
- Available through Health Canada Special Access Program for pts that aren't able to respond to alternative therapies

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Glitazones

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Rosiglitazone/Pioglitazone

- Class
  - Thiazolidinedione
- Approved Indications
  - Diabetes
- NOC:
  - March and August 2000

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Health Canada Endorsed Important Safety Information on Pr AVANDIA®, Pr AVANDAMET® and Pr AVANDARYL™

GlaxoSmithKline

February 23, 2007

Dear Health Care Professional:

Subject: Increased Incidence of Fractures in Female Patients Who Received Long-Term Treatment with AVANDIA® (rosiglitazone maleate) Tablets for Type 2 Diabetes Mellitus

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/avandia_hpc-cps_3_e.html

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Health Canada Endorsed Important Safety Information on Pr ACTOS® (pioglitazone hydrochloride)

Lilly

April 18, 2007

Dear Health Care Professional:

Subject: **Increased Incidence of Fractures in Female Patients Who Received Long-Term Treatment with ACTOS® (pioglitazone hydrochloride) Tablets for Type 2 Diabetes Mellitus**

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/actos_hpc-cps_2_e.html

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Fracture Rates

- 2 observational cohort studies
- 1 RCT in healthy volunteers
- 1 RCT in diabetic patients
- Unpublished data

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Thiazolidinedione Use and Bone Loss in Older Diabetic Adults

- Analysis of 4 yr data from Health, Aging, and Body Composition Observational study
- 666 diabetic patients
  - 69 reported TDZ use
    - Troglitazone N=22
    - Pioglitazone N=30
    - Rosiglitazone N=31
- Significantly greater bone loss seen in ♀
  - 0.67% whole body (p<0.001)
  - 1.14% lumbar spine (p=0.004)
  - 0.65% trochanter (p=0.016)

J Clin Endocrinol Metab 2006;91: 3349-3354.

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Thiazolidinedione Treatment Decreases Bone Mineral Density in Type 2 Diabetic Men

- Retrospective cohort study
- 32 ♂ on rosiglitazone 4mg BID matched to 128 ♂
- Results:
  - Greater loss shown in:
    - Hip: -1.19% vs -0.137% (p=0.006)
    - Femoral Neck: -1.22% vs 0.20% (p= 0.0001)
  - Less BMD gain in:
    - Spine: +0.69% vs +2.3% (p=0.03)

Diabetes Care 2007; 30(6): 1574-1576

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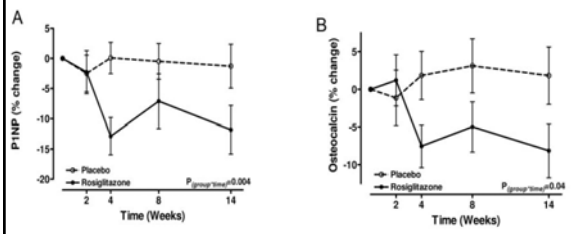
The Peroxisome Proliferator-Activated Receptor-γ Agonist Rosilgitazone Decreases Bone Formation and Bone Mineral Density in Healthy Postmenopausal Women: A Randomized, Controlled Trial

- Objective:
  - To determine whether rosiglitazone inhibits bone formation.
- Design:
  - 14 wk R, DB, PC
- Population:
  - 50 healthy, postmenopausal women
- Intervention:
  - Rosiglitazone 8mg/day

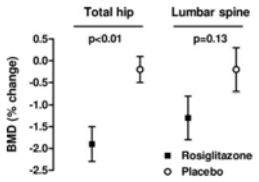
J Clin Endocrinol Metab 2007; 92: 1305-1310.

Primary Outcome



J Clin Endocrinol Metab 2007; 92: 1305-1310.

Secondary Outcome



J Clin Endocrinol Metab 2007; 92: 1305-1310.

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

	Rosiglitazone	Metformin	Glyburide
	number of patients (percent)		
Men	32 (3.95)	29 (3.36)	28 (3.35)
Women	60 (9.30)	30 (5.08)*	21 (3.47)*
Lower limb	36 (5.58)	18 (3.05)†	8 (1.32)*
Upper limb	22 (3.41)	10 (1.69)	9 (1.49)†
Spinal	1 (0.16)	1 (0.17)	1 (0.17)

* P<0.01 for the comparison with rosiglitazone (unadjusted, contingency chi-square test).
† P<0.05 for the comparison with rosiglitazone (unadjusted, contingency chi-square test).

N Engl J Med 2006; 355: 2427-43.

Unpublished Data

- Analysis of 19 trials showed pioglitazone in females had increased event of bone fracture
  - 2.6% vs 1.7%
- Fractures occurred most frequently in:
  - Distal upper limb (forearm, hand, wrist)
  - Distal lower limb (foot, ankle, fibula, tibia)

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/actos_hpc-cps_2_e.html

Proposed Mechanism

- PPARγ receptors present in mesenchymal stem cells in bone marrow
- Stimulation of mesenchymal cells may lead to preferential differentiation to marrow adipocytes over osteoblasts
- Also inhibitory effect on estrogen and androgen biosynthesis may induce bone loss

Ann Pharmacother 2007; 41

Health Canada Endorsed Important Safety Information on rosiglitazone (PrAVANDIA®, PrAVANDAMET® and PrAVANDARYL™)

November 1, 2007

Dear Health Care Professional:

Subject: **New restrictions on the use of rosiglitazone products due to cardiac safety concerns (AVANDIA®, AVANDAMET® and AVANDARYL™)**

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/avandia_hpc-cps_5_e.html

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Health Canada Endorsed Important Safety Information on PrAVANDIA®, PrAVANDAMET® and PrAVANDARYL™

June 1, 2007

Dear Health Care Professional:

Subject: **Cardiac Safety of Avandia® (rosiglitazone maleate).**

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/avandia_hpc-cps_4_e.html

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Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

- Objective
  - To assess the effect of rosiglitazone on cardiovascular outcomes.
- Selection Criteria
  - Search Strategy
    - Published literature, FDA website, GlaxoSmithKline clinical trials registry
  - Inclusion Criteria
    - Randomized comparator group, similar duration of treatment, >24 wks drug exposure

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N Engl J Med 2007; 356

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

- 42 trials included
- Mean age = 56 yrs
- Mean HbA1C = 8.2%
- Results
  - Myocardial Infarction
    - 1.43 (95% CI 1.03 – 1.98; p=0.03)
  - Death from Cardiovascular Causes
    - 1.64 (95% CI 0.98 – 2.74; p=0.06)

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N Engl J Med 2007; 356

Rosiglitazone Evaluated for Cardiovascular Outcomes – An Interim Analysis.

- Unplanned interim analysis
- R, MC, Open-label, noninferiority trial
- N = 4447 pts w/ Type II DM
- Metformin + Rosiglitazone OR Sulfonylurea

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N Engl J Med 2007; 357: 28-38.

Table 2. Hospitalization or Death from Cardiovascular Causes.*

Variable	Rosiglitazone Group (N = 2220)	Control Group (N = 2227)	Hazard Ratio (95% CI)	P Value
	no. of patients			
Adjudicated events				
Primary end point	217	202	1.08 (0.89–1.31)	0.43
Death				
From cardiovascular causes†	29	35	0.83 (0.51–1.36)	0.46
From any cause	74	80	0.93 (0.67–1.27)	0.63
Acute myocardial infarction‡	43	37	1.16 (0.75–1.81)	0.50
Congestive heart failure‡	38	17	2.24 (1.27–3.97)	0.006
Death from cardiovascular causes, myocardial infarction, and stroke	93	96	0.97 (0.73–1.29)	0.83
Events adjudicated and pending adjudication				
Primary end point	267	243	1.11 (0.93–1.32)	0.26
Death				
From cardiovascular causes†	37	46	0.80 (0.52–1.24)	0.32
Acute myocardial infarction‡	49	40	1.23 (0.81–1.86)	0.34
Congestive heart failure‡	47	22	2.15 (1.30–3.57)	0.003
Death from cardiovascular causes, myocardial infarction, and stroke	109	114	0.96 (0.74–1.24)	0.74

N Engl J Med 2007; 357: 28-38.

Long-term Risk of Cardiovascular Events with Rosiglitazone. A Meta-analysis

- Objective
  - To systematically review current evidence or risks of MI, heart failure, & CV mortality w/ long-term rosiglitazone use.
- Selection Criteria
  - Search Strategy
    - Medline, GlaxoSmithKline clinical trials register, US FDA, product information sheets
- Inclusion Criteria
  - Intention to monitor CV events; RCT ≥ 12 mos; IGT or DM2; control either active or placebo

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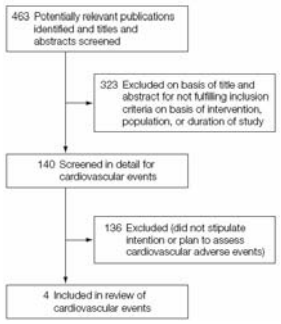
JAMA 2007; 298(10): 1189-1195.

Long-term Risk of Cardiovascular Events with Rosiglitazone. A Meta-analysis



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JAMA 2007; 298(10): 1189-1195.

Long-term Risk of Cardiovascular Events with Rosiglitazone. A Meta-analysis

- Myocardial Infarction
  - RR 1.42 (95% CI 1.06-1.91, p=0.02)
- Heart Failure
  - RR 2.09 (95% CI 1.52-2.88, p<0.001)
- Cardiovascular Mortality
  - RR 0.90 (95% CI 0.63-1.26, p=0.53)

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JAMA 2007; 298(10): 1189-1195.

Glitazone Conclusion

- Bone Loss
  - Educate pts on risk
- Cardiovascular
  - Rosiglitazone
    - not approved for monotherapy unless metformin CI
    - no longer to be used w/ sulfonylurea unless metformin CI
  - Rosiglitazone contraindicated in pts w/ any stage of heart failure.

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Adverse Drug Reaction Reporting

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Current State of Drug Development

- Phase I
  - Assess drug's safety in healthy volunteers
- Phase II
  - Studied in a larger population to determine efficacy.
- Phase III
  - Used to confirm efficacy, monitor side effects, compare to current treatments.
- Phase IV
  - Studies completed after a drug has been marketed

www.centerwatch.com; http://www.nlm.nih.gov/services/ctphases.html

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Drug Development - US

- 51% of drugs have label changes due to safety issues discovered post-marketing
- 20% of drugs get black box warnings after marketing
- 3-4% of drugs are withdrawn from the market for safety reasons

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JAMA 2006; 295(17): 2072-2075.

Canadian and US Drug Approval Times and Safety Considerations

- Objective:
  - To compare new drug approval times in Canada and the US over a 10-year period and to relate them to safety discontinuations.
- Results:
  - Median approval time in Canada 200 days longer ($p<0.0001$)
  - 3.6% in US vs 2.0% in Canada withdrawn secondary to safety

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Ann Pharmacother 2003; 37: 1403-8.

Post-Marketing Surveillance

- Anecdotal reporting
- Voluntary spontaneous reporting
- Intensive event monitoring
- Cohort studies
- Case-control studies
- Population statistics
- Record linkage
- Meta-analysis

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Lancet 2000; 356: 1255-59.

Table 1: Number and percentage of adverse reaction reports by source of report, 1999-2004

Source	1999	2000	2001	2002	2003	2004
Pharmacist	2103 (37.0)	2420 (32.9)	2097 (28.4)	2141 (25.0)	2369 (25.7)	3011 (29.4)
Physician	1446 (25.4)	1876 (25.5)	1914 (25.9)	2093 (24.4)	2176 (23.6)	2667 (26.2)
Health professional*	1051 (18.5)	1157 (15.7)	1378 (18.6)	1780 (20.8)	1974 (21.4)	1499 (14.6)
Consumer or patient	516 (9.1)	1010 (13.7)	1102 (14.9)	1581 (18.5)	1628 (17.7)	1928 (18.8)
Nurse	447 (7.9)	381 (5.2)	443 (6.0)	421 (4.9)	689 (7.5)	873 (8.5)
Other	125 (2.2)	517 (7.0)	455 (6.2)	550 (6.4)	373 (4.1)	260 (2.5)
Total	5688 (100)	7361 (100)	7389 (100)	8566 (100)	9209 (100)	10 238 (100)
Change from previous yr, %	-	29.4	0.4	15.9	7.5	11.2

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CMAJ 2006; 174(2): 191-192.

Limitations of Spontaneous Reporting

- Reliance on voluntary reporting
- Poor quality of submitted reports
- Underreporting of adverse outcomes
- Incomplete numerator and denominator data
- Difficulty establishing causal effect

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JAMA 2004; 292(21): 2647-2650.

Re-examining our approach to the approval and use of new drugs.

- Avoid using new drugs when older, reliable alternatives are available
- Inform pts of limited safety data on new drugs and alert them to possible AEs
- Include approval date on labelling of new drugs
- Encourage AE reporting
- Independent surveillance system should be required for new drugs
- Higher regulatory threshold for new drugs if safe and efficacious alternatives already exist

60

CMAJ 2006; 174(13): 1855.

Resources

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Questions

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References (General)

- Edwards RI, Aronson JK. Adverse drug reactions: definitions, diagnosis and management. Lancet 2000; 356: 1255-59.
- Lee SK. Re-examining our approach to the approval and use of new drugs. CMAJ 2006; 174(13): 1855.
- Fontanarosa PB, Rennie D, DeAngelis CD. Postmarketing Surveillance – Lack of Vigilance, Lack of Trust. JAMA 2004; 292(21): 2647-2650.
- Brewer T, Colditz GA. Postmarketing Surveillance and Adverse Drug Reactions. Current perspective and future needs. JAMA 1999; 281: 824-829.
- Strom BL. How the US Drug Safety System Should be Changed. JAMA 2006; 295(17): 2072-4.
- Rawson NSB, Kaitin KI. Canadian and US Drug Approval Times and Safety Considerations. Ann Pharmacother 2003; 37: 1403-8.
- Lexchin J. Is there still a role for spontaneous reporting of adverse drug reactions? CMAJ 2006; 174(2): 191-192.
- Trontell A. Expecting the Unexpected – Drug Safety, Pharmacovigilance and the Prepared Mind. N Engl J Med; 351(14): 1385-1387.
- www.centerwatch.com
- http://www.nlm.nih.gov/services/ctphases.html

65

References (Telithromycin)

- Clay KD, Hanson JS, Pope SD et al. Brief Communication: Severe Hepatotoxicity of Telithromycin: Three Case Reports and Literature Review. Ann Intern Med 2006; 144: 415-20.
- Graham DJ. Telithromycin and Acute Liver Failure. N Engl J Med 2006; 355(21): 2260-1.
- Turner M. Corey GR, Abrutyn E. Telithromycin. Ann Intern Med 2006; 144: 447-8.
- Zhanel GG, Walters M, Noreddin A et al. The Ketolides A Critical Review. Drugs 2002; 62(12): 1771-1804.
- Ross DB. The FDA and the Case of Ketek. N Engl J Med 2007; 356(16): 1601-4.
- www.pmprb-cepmb.gc.ca
- www.sanofi-aventis.ca
- http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/ketek_hpc-cps_e.html
- http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/ketek_2_hpc-cps_e.html

66

References (Pergolide)

- Schade R, Andersohn F, Suissa S et al. Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation. N Engl J Med 2007; 356: 29-38.
- Zanettini R, Antonini A, Gatto G et al. Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease. N Engl J Med 2007; 356: 39-46.
- Roth BL. Drugs and Valvular Heart Disease. N Engl J Med 2007; 356(1): 6-9.
- Rascol O, Pathak A, Bagheri H et al. New Concerns about Old Drugs: Valvular Heart Disease on Ergot Derivative Dopamine Agonists as an Exemplary Situation of Pharmacovigilance. Movement Disorders 2004; 19(6): 611-3.
- Waller EA, Kaplan J, Heckman MG. Valvular Heart Disease in Patients Taking Pergolide. Mayo Clin Proc 2005; 80(8): 1016-1020.
- Van Camp G, Flamez A, Cosyns B et al. Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. Lancet 2004; 363: 1179-83.
- http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/permax_3_hpc-cps_e.html

References (Pergolide)

- Flowers CM, Racoosin JA, Lu SL et al. The US Food and Drug Administration's Registry of Patients with Pergolide-Associated Valvular Heart Disease. Mayo Clin Proc 2003; 78: 730-1.
- Horvath J, Fross RD, Kleiner-Fisman G et al. Severe Multivalvular Heart Disease: A New Complication of the Ergot Derivative Dopamine Agonists. Movement Disorders 2004; 19(6): 656-662.
- Pritchett AM, Morrison JF, Edwards WD et al. Valvular Heart Disease in Patients Taking Pergolide. Mayo Clin Proc 2002; 77: 1280-1286.
- Van Camp G, Flamez A, Cosyns B et al. Heart valvular disease in patients with Parkinson's disease treated with high-dose pergolide. Neurology 2003; 61: 859-861.
- Baseman DG, O'Suilleabhain PE, Reimold SC et al. Pergolide use in Parkinson disease is associated with cardiac valve regurgitation. Neurology 2004; 63: 301-4.

References (Glitazones)

- Singh S, Loke YK, Furberg CD. Long-term Risk of Cardiovascular Events with Rosiglitazone. JAMA 2007; 298(10): 1189-1195.
- Horne PD, Pocock SJ, Beck-Nielsen H et al. Rosiglitazone Evaluated for Cardiovascular Outcomes – An Interim Analysis. N Engl J Med 2007; 357: 28-38.
- Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. N Engl J Med 2007; 356
- Diamond GA, Bax L, Kaul S. Uncertain Effects of Rosiglitazone on the Risk for Myocardial Infarction and Cardiovascular Death. Ann Intern Med 2007; 147: 578-581.
- Murphy CE, Rodgers PT. Effects of Thiazolidinediones on Bone Loss and Fracture. Ann Pharmacother 2007; 41.
- Rosen CJ. The Rosiglitazone Story – Lessons from an FDA Advisory Committee Meeting. N Engl J Med 357; 9: 844-6.
- Psaty BM, Furberg CD. The Record on Rosiglitazone and the Risk of Myocardial Infarction. N Engl J Med 357; 1: 67-9.

References (Glitazones)

- Meymeh RH, Wooltorton E. Diabetes drug pioglitazone (Actos): risk of fracture. CMAJ 2007; 177(7): 723-724.
- http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/avandia_hpc-cps_3_e.html
- http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/actos_hpc-cps_2_e.html
- Schwartz AV, Sellmeyer DE, Vittinghoff E. et al. Thiazolidinedione Use and Bone Loss in Older Diabetic Adults. J Clin Endocrinol Metab 2006;91: 3349-3354.
- Yaturu S, Bryant B, Jain SK. Thiazolidinedione Treatment Decreases Bone Mineral Density in Type 2 Diabetic Men. Diabetes Care 2007; 30(6): 1574-1576.
- Grey A, Bolland M, Gamble G et al. The Peroxisome Proliferator-Activated Receptor-γ Agonist Rosilgitazone Decreases Bone Formation and Bone Mineral Density in Healthy Postmenopausal Women: A Randomized, Controlled Trial. J Clin Endocrinol Metab 2007; 92: 1305-1310.
- Kahn SE, Haffner SM, Heise MA et al. Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. N Engl J Med 2006; 355: 2427-43.
- http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/actos_hpc-cps_2_e.html
- http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/avandia_hpc-cps_5_e.html
- http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/avandia_hpc-cps_4_e.html

